Probing the influence of SMA and vmPFC on the motor system with dual-site transcranial magnetic stimulation

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Abstract

Dual-site transcranial magnetic stimulation (TMS) has been widely exploited to probe the influence of cortical structures on the primary motor cortex (M1). However, several issues remain open, notably regarding the use of this approach on areas of the medial frontal cortex – including the supplementary motor area (SMA) and the ventromedial prefrontal cortex (vmPFC) – known to play a fundamental role in motor behavior. First, the few TMS studies that have targeted SMA have mostly focused on short inter-stimulation intervals (6-8 ms), supposed to recruit cortico-cortical circuits. There is a current lack of data on the nature of the influence (*i.e.*, facilitatory *vs.* suppressive) of SMA stimulation on M1 when probed with longer intervals (10-15 ms), thought to recruit more indirect cortico-subcortico-cortical circuits. Second, it is unclear whether the facilitatory influence of SMA stimulation previously reported with short intervals reflects the recruitment of cortico-cortical circuits (as commonly assumed) or results from the summation of volleys descending from SMA and M1 at the spinal level. Third, dual-site TMS has never been used to date to probe the influence of the vmPFC on M1, putatively due to the presumed difficulty of reaching the former area with magnetic fields. Here, we show that SMA stimulation facilitates motor activity with a 12 ms interval. Additionally, our data reveal that the facilitatory influence of SMA stimulation observed with short intervals does not result from spinal interactions. Finally, we show that vmPFC stimulation induces a moderate suppressive effect on M1, both with short and with long inter-stimulation intervals.

Introduction

The execution of most volitional actions relies on pyramidal cells located in the primary motor cortex (M1), which project down to the spine and connect with peripheral motoneurons. This so-called corticospinal pathway is under the constant influence of distributed areas of the cerebral cortex, relying on effective connectivity to either facilitate or suppress M1 activity and, ultimately, exert control over behavior. As such, two key areas of the medial frontal cortex– the supplementary motor area (SMA) and the ventromedial prefrontal cortex (vmPFC) – are known to play a central role in human behavior, being involved in processes as diverse as motor planning (Carlsen et al. 2015; Makoshi et al. 2011; Neige et al. 2018), decision-making (Fellows 2007; Klein-Flugge et al. 2016; Nogueira et al. 2017) and inhibitory control (Aron et al. 2007; Boy et al. 2010; Hu and Li 2012). SMA and vmPFC project to M1 through both cortico-cortical and cortico-subcortico-cortical circuits, providing candidate routes through which they could implement these processes. Crucially though, tools to probe their effective influence on M1 remains scarce at present.

In humans, a particular type of transcranial magnetic stimulation (TMS) protocol – called dual-site paired-pulse TMS (ppTMS) – allows probing effective connectivity between specific cortical areas and M1 (for recent reviews, see Derosiere and Duque 2020; Neige et al. 2021). As such, the excitability of the corticospinal pathway can be quantified through the recording of motor-evoked potentials (MEPs), which can be elicited in muscles by applying single-pulse TMS over the contralateral M1. The amplitude of MEPs provides a global readout of corticospinal excitability, reflecting the simultaneous influence of multiple brain structures projecting onto M1 (Bestmann and Duque 2016; di Lazzaro et al. 2018). Dual-site ppTMS allows isolating the influence of a targeted cortical area on M1. In such protocols, a first, conditioning stimulation is exploited to pre-activate the targeted area, while a second, test stimulation is applied over M1 with another coil to elicit a MEP and assess the nature of the influence (*i.e.*, facilitatory or suppressive) of the pre-activated area on corticospinal excitability. The potentiation of conditioned MEP amplitudes (*i.e.*, relative to unconditioned MEPs) reflects a facilitarory influence of the pre-activated area, while a reduction of conditioned MEPs reflects a suppressive effect. Interestingly, varying the inter-stimulation interval allows probing different circuits, with short inter-stimulation intervals (*e.g.*, between 4 and 8 ms) recruiting cortico-cortical circuits preferentially, and longer ones (*e.g.*, higher than 10 ms) recruiting more indirect circuits presumably funneling through subcortical structures (Neubert et al. 2010).

Over the last two decades, dual-site ppTMS has been widely exploited in humans, with studies probing the causal influence of multiple areas of the premotor cortex (Davare et al. 2008; Koch et al. 2006), of the lateral prefrontal cortex (Neubert et al. 2010; Wang et al. 2020) and of the parietal cortex on M1 (Allart et al. 2019; Koch et al. 2009; Koch and Rothwell 2009; Lebon et al. 2012; Vesia et al. 2017). However, several issues remain open, notably concerning the use of this approach on some areas of the medial frontal cortex – including SMA and vmPFC.

So far, the few ppTMS studies that have targeted SMA have mostly focused on short inter-stimulation intervals (6 to 8 ms, Arai et al. 2011, 2012; Green et al. 2018; Rurak et al. 2021). Given this, there is a current lack of data on the nature of the influence (*i.e.*, facilitatory *vs*. suppressive) of SMA stimulation on M1 activity when probed with longer inter-stimulation intervals (*i.e.*, 10 to 15 ms). In fact, SMA projects to M1 through multiple cortico-subcortico-cortical circuits (Nachev et al. 2008), with some exerting a net facilitatory influence on motor activity (*e.g.*, the direct pathway of the basal ganglia) and others playing a suppressive role (*e.g.*, the indirect and hyperdirect pathways). Interestingly, ppTMS studies focusing on the preSMA – *i.e.*, another key area of the medial frontal cortex – with intervals of 12 ms, reported a potentiation of conditioned MEP amplitudes, which strongly covaried with white matter density in preSMA-basal ganglia-M1 circuits (Mars et al. 2009; Neubert et al. 2010). Together, these two sets of findings suggest that, when applied over preSMA with such intervals, ppTMS recruits circuits that bear a facilitatory influence on M1 and funnel through the basal ganglia. A first goal of the present study is to provide insights as regards to the influence of SMA stimulation on M1 with such intervals, by testing the idea that SMA-originating circuits bear a similar facilitatory influence on motor activity.

As such, ppTMS studies that have targeted SMA with short inter-stimulation intervals (6 to 8 ms) reported a potentiation of MEP amplitudes, which has been assumed to reflect the operation of cortico-cortical, facilitatory circuits from SMA to M1 (Arai et al. 2011, 2012; Green et al. 2018; Rurak et al. 2021). This assumption seems indeed consistent with animal studies showing that SMA presents direct glutamatergic projections to M1 (Luppino et al. 1993; Muakkassa and Strick 1979) and that electrical stimulation of SMA neurons evokes responses in M1 with short latencies, of about 4 ms (Aizawa and Tanji 1994; Tokuno and Nambu 2000). Importantly though, other observations question the validity of this assumption. Indeed, like M1, SMA also presents pyramidal cells that project to the spine (Dum and Strick 1996) and in specific contexts, a unique stimulation of SMA with single-pulse TMS can evoke MEPs

(Entakli et al. 2014; Spieser et al. 2013), indicating that these pyramidal cells can also recruit motoneurons. Thus, it is possible that the MEP potentiation reported in ppTMS studies using short intervals reflects the summation of volleys descending from SMA and M1 and converging at close times on motoneurons. In other words, it is currently unclear whether this potentiation can be taken as a pure measure of effective connectivity between SMA and M1 or not. Addressing this issue is fundamental for any investigation targeting motor areas (*e.g.*, the dorsal or the ventral premotor cortex; Davare et al. 2009, Koch et al. 2006), which, for the most part, present corticospinal projections (Dum and Strick 1991). This represents the second goal of the current study. Specifically, we tested the effect of SMA conditioning on MEP amplitudes using a very short inter-stimulation intervals of 1 ms. The rationale here is that a 1 ms interval would be too short for a MEP potentiation to result from the recruitment of cortico-cortical circuits (Aizawa and Tanji 1994; Tokuno and Nambu 2000); any potentiation occurring with this interval would instead provide evidence for a summation of neural inputs occurring at the spinal level.

As mentioned earlier, vmPFC represents another major area of the medial frontal cortex (Amodio and Frith 2006). Strikingly though, ppTMS has never been used to date to probe the influence of this area on M1, putatively due to the presumed difficulty of reaching it with magnetic fields. As such, a few repetitive TMS investigations have attempted to target vmPFC and produced mixed findings, with some succeeding in altering behavior (Kearney-Ramos et al. 2018) and others failing to do so (Codol et al. 2020). Hence, it is currently unknown whether TMS could be exploited to probe effective connectivity between vmPFC and M1 and, relatedly, what would be the nature of the influence of the recruited circuits on motor activity. In fact, while former investigations on caudal areas of the medial frontal cortex (*i.e.*, SMA and preSMA) generally reported a facilitatory influence on M1, ppTMS studies on more rostral areas of the frontal lobe, such as the dorsolateral PFC, revealed the operation of suppressive circuits (Wang et al. 2020). A third goal of the present study is to test the feasibility of exploiting ppTMS to probe effective connectivity between vmPFC and M1 and, relatedly, to determine the influence of vmPFC stimulation on M1 activity.

Overall, the current study addresses three major goals. The first one is to provide insights as regards to the influence of SMA stimulation on M1 activity with long inter-stimulation intervals, presumed to recruit cortico-subcortico-cortical circuits. As a second objective, we aim to clarify whether the MEP potentiation reported in studies targeting SMA and M1 with short intervals can be taken as a pure measure of cortico-cortical connectivity between these

areas or if it could in part reflect the summation of volleys descending from those on motoneurons. Finally, we seek to test the feasibility of exploiting ppTMS to probe effective connectivity between vmPFC and M1 and, relatedly, to determine the influence of vmPFC stimulation on motor activity.

Material and Methods

Participants

Twenty healthy subjects participated in the current study (13 females; mean age 26.9 years ± 5.4; right-handed as assessed by the Edinburgh Handedness Inventory (Oldfield 1971)). Subjects were recruited from the Research Participant Pool at the Institute of Neuroscience of the Catholic University of Louvain (Brussels, Belgium). None of them had any neurological disorder, history of psychiatric illness or drug or alcohol abuse, or presented any contraindication to TMS (Rossi et al. 2009, 2011). Subjects provided written informed consent before the start of the experiment and received a financial compensation for their participation. The protocol was approved by the institutional review board of the Catholic University of Louvain and complied with the principles of the Declaration of Helsinki.

Transcranial magnetic stimulation protocol

Coil locations

Dual-site ppTMS involves applying a test stimulation (TS) with one coil over M1 preceded, in a certain proportion of trials, by a conditioning stimulation (CS) delivered with another coil over an area of interest. Our aim here was to investigate intra-hemispheric influences of SMA and vmPFC on M1. To do so, we applied both stimulations over the left, dominant hemisphere, with the TS administered over the left M1 and the CS targeting either the left SMA or the left vmPFC in separate blocks of trials. TS and CS were delivered with two small figure-of-eight coils (Magstim D25-Alpha model; wing internal diameter: 35 mm) connected to two monophasic Magstim stimulators (200^2 and $Bistim^2$ stimulators; Magstim, Whitland, Dyfed, UK).

M1 coil

The M1 coil was placed tangentially to the scalp with the handle pointing backward and laterally at a 45° angle away from the midsagittal line, resulting in a postero-anterior current flow within the cortex (Derosiere et al. 2020; Rossi et al. 2009; Rossini et al. 1994). To define the optimal site for M1 stimulation (*i.e.*, the so-called "hotspot"), we relied on markers disposed on an electroencephalography (EEG) cap fitted on the participant's head (Vandermeeren et al. 2009). Of note, due to the anatomical proximity of left M1 and left SMA, in a number of subjects (n = 12 / 20), the position of the M1 coil had to be slightly adjusted when the SMA coil was settled over the scalp; this position was exploited for TS during SMA blocks. Hence, we defined two different positions for M1 stimulation: the real hotspot and an adjusted hotspot.

To find the real hotspot, we first applied the stimulation with the center of the M1 coil over the C3 location of the EEG cap (*i.e.*, corresponding to the left M1 area Alamia et al. 2019; Derosiere et al. 2018), in the absence of the second coil on the head. Stimulation intensity was increased until consistent MEP responses were obtained in the right first dorsal interosseous (FDI) muscle at this location. We then moved the coil by steps of ~ 0.5 cm around this location in both the rostrocaudal and the mediolateral axes. Stimulation was applied with the previously defined intensity at each new location, and MEP amplitudes were visually screened. The real hotspot was defined as the location at which the largest and most consistent MEP amplitudes could be obtained (Derosiere et al. 2019; Neige et al. 2018; Rossini et al. 1994). The coil was then held at this location, and the edges of its shape were marked on tapes disposed on the EEG cap. These marks allowed us to localize the real hotspot at any required time during the session. To determine the adjusted hotspot, we first positioned the SMA coil over the head and then reproduced the same procedure as described above, while trying to fit the two coils over the head. Once the largest MEP amplitudes obtained, the two coils were held at their respective locations, and the edges of the M1 coil were marked on the EEG cap. These marks allowed us to localize the adjusted hotspot during SMA blocks.

SMA and vmPFC coils

To ensure that the coil exploited for the CS was precisely targeting SMA and vmPFC in each subject, we exploited neuronavigation. To this end, subjects underwent a T1-weighted high-resolution anatomical magnetic resonance imaging (MRI) prior to participating in the TMS experiment (1.5 T; Achieva, Philips Healthcare, Eindhoven, The Netherlands). We then

determined the SMA and vmPFC locations on the individual images using MNI coordinates in a dedicated software (Visor 2.0 Advanced NeuroTechnologies, Enschede, Netherlands). The locations were finally used during the experiment, in which we relied on head and coil trackers as well as a 3D tracking device to coregister the position of the SMA/vmPFC coil with the individual MRI.

The MNI coordinates exploited to initially localize SMA and vmPFC were x = -8, y = -9, z = 77 and x = − 7, y = 71, z = -4, respectively (Codol et al. 2020). These two locations were then slightly adjusted for each subject using the Visor software, so that they corresponded to the point where the scalp-to-cortex distance was minimal. Following this procedure, the MNI coordinates for SMA and vmPFC locations were x = -7.9 ± 0.3, y = -7.4 ± 0.8, z = 82.9 ± 1 and x = -9.4 ± 0.7, y = 72.6 ± 0.5, z = 8.2 ± 1.7, respectively (mean ± standard error (SE) of the group; see Figure 1 and Table 1 for group-averaged and individual MNI coordinates, respectively).

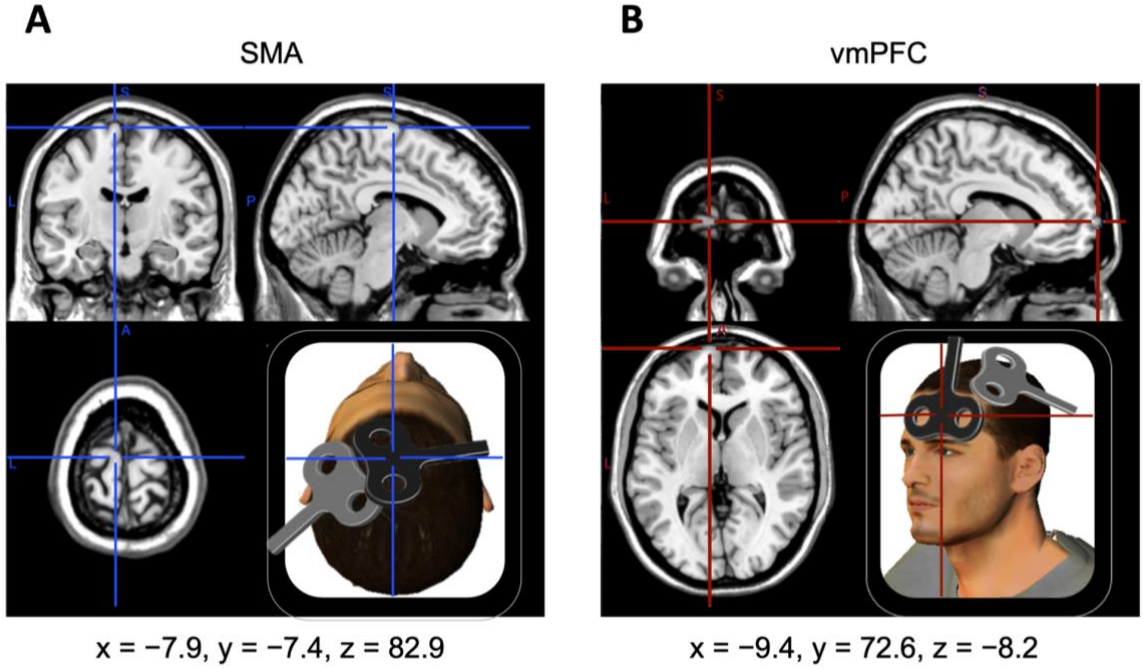

Figure 1: Localization of the sites of stimulation and illustration of the coil positioning for SMA (A) and vmPFC (B) targets. The group-averaged MNI coordinates are illustrated on a standard MRI template (coronal, sagittal and axial views) using MRIcron software (v1.0.20190902, http://www.mricro.com).

Subject	SMA coordinates			vmPFC coordinates		
	x	y	z	x	y	z
1	-6	-7.7	84.2	-7.1	72.5	21.7
2	-7.6	-9.4	76.2	-8.1	70.3	-1.7
3	-8	-2.5	80.6	-10.3	73.2	2.6
4	-8	-8.9	77.8	-17.7	70.8	7.5
5	-6.9	-8.8	88.6	-14.5	73.4	25.4
6	-7.9	-7.4	82.3	-9.4	72.6	8.2
7	-11.9	-8.1	81.7	-9	65.3	19
8	-7.8	-1.6	88	-13.3	73	9.7
9	-8.3	-9.9	86.1	-10	76	6.3
10	-7.5	-10	86.2	-10.7	73.7	4
11	-7.5	-6.6	79.7	-9.9	72.5	12.9
12	-7.6	-5.4	86.3	-8.4	69.7	3.4
13	-10.4	2.1	74.3	-8.7	72.8	-1.1
14	-8	-9.8	76.3	-5.8	72.9	2.6
15	-6.7	-10.6	84.9	-8	70.9	3.7
16	-8.3	-10.5	84.9	-7.3	73.5	11.1
17	-7.4	-6	79.9	-6.4	73.9	8.1
18	-7.6	-10.9	85.4	-8.5	76	9.6
19	-7.2	-7.1	85.7	-8.5	73.8	5.8
20	-7.8	-9.6	88.4	-5.9	74.8	5.8
Mean	**-7.9**	**-7.4**	**82.9**	**-9.4**	**72.6**	**8.2**
SE	**0.3**	**0.8**	**1**	**0.7**	**0.5**	**1.7**

Table 1: Individual MNI coordinates for SMA and vmPFC target locations. The MNI coordinates exploited to initially localize SMA and vmPFC were x = -8, y = -9, z = 77 and x = − 7, y = 71, z = -4, respectively. These two locations were then slightly adjusted for each subject using the Visor software, so that they corresponded to the point where the scalp-to-cortex distance was minimal.

For both SMA and vmPFC stimulation, the center of the coil was placed over the corresponding target location (see Figure 1). In SMA blocks, the coil was held tangential to the scalp with the handle pointing at a -100° angle away from the midsagittal line (*i.e.*, in the counter-clockwise direction), resulting in a medio-lateral current flow within the cortex (Figure 1). This coil position was chosen based on a previous experiment showing that it allows the most optimal recruitment of SMA neurons (Arai et al. 2012). In vmPFC blocks, the coil was held tangential to the forefront with the handle directed upward and parallel to the midsagittal line (Codol et al. 2020), resulting in a downward current flow at the cortical level.

Stimulation intensities

Once the real and the adjusted hotspots were found (see above), we determined the resting motor threshold (rMT) for both locations. The rMT was defined as the lowest stimulation intensity (expressed in percentage of maximal stimulator output (%MSO)) required to evoke MEPs of 50 µV amplitude on 5 out of 10 consecutive trials in the relaxed FDI muscle (Rossini et al. 1994, 2015). The rMTs for the real and the adjusted hotspots were 39.9 ± 1.5 % and 44.6 ± 1.9 %MSO, respectively (see Table 2 for individual rMT values).

Subject	Real hotspot rMT (%MSO)	Adjusted hotspot rMT (%MSO)
1	37	37
2	31	37
3	36	45
4	39	39
5	45	55
6	51	59
7	50	54
8	40	45
9	31	31
10	37	37
11	42	42
12	35	44
13	57	65
14	41	41
15	35	35
16	38	46
17	43	48
18	38	42
19	41	49
20	39	39
Mean	**39.9**	**44.6**
SE	**1.5**	**1.9**

Table 2: Resting motor threshold (rMT) expressed in percentage of maximal stimulator output (%MSO) obtained for each subject using the real and adjusted hotspots. Subjects for whom the hotspot had to be adjusted (12/20 subjects) are highlighted in black.

These rMT values were exploited to determine the stimulation intensities to be used for the rest of the experiment. In SMA blocks, the M1 coil was positioned over the adjusted hotspot. Hence, we based on the rMT obtained at this location to define the stimulation intensity for M1; we stimulated M1 at 120 % of this rMT. Conversely, in vmPFC blocks, the M1 coil could be easily positioned over the real hotspot and we thus stimulated at 120 % of the rMT obtained for

the real hotspot. Finally, CS intensity was set at 120 % of the rMT obtained for the real hotspot, both in SMA and in vmPFC blocks (Brown et al. 2019).

Inter-stimulation intervals and blocks

As mentioned in the Introduction section, the goal of the present study was threefold. First, we aimed to test the influence of SMA stimulation on M1 activity with long inter-stimulation intervals, presumed to recruit cortico-subcortico-cortical circuits. To this aim, we exploited intervals of 12 and 15 ms (Neubert et al., 2010). As a second objective, we sought to clarify whether the MEP potentiation reported in studies targeting SMA and M1 with short intervals (Arai et al. 2011, 2012; Green et al. 2018; Rurak et al. 2021) can be taken as a pure measure of cortico-cortical connectivity between these areas or if it could in part reflect the summation of volleys descending from those on motoneurons. To address this issue, we tested the effect of SMA conditioning on MEP amplitudes using a very short inter-stimulation intervals of 1 ms. The rationale here was that a 1 ms interval would be too short for a MEP potentiation to result from the recruitment of cortico-cortical circuits (Tokuno and Nambu, 2000; Aizawa and Tanji, 1994); any potentiation occurring with this interval would instead provide evidence for a summation of neural inputs occurring at the spinal level. We also included other short inter-stimulation intervals of 4, 6 and 8 ms in the experiment to be able to compare the effect obtained on MEP amplitudes when using the 1 ms interval *vs.* when exploiting more classical intervals. Finally, we aimed to test the feasibility of exploiting ppTMS to probe effective connectivity between vmPFC and M1 and, relatedly, to determine the influence of vmPFC stimulation on motor activity. Given the current lack of data regarding the latter issue, we exploited all of the intervals mentioned above in vmPFC blocks too. Note that, contrary to SMA, vmPFC does not present corticospinal projections. Hence, the use of a 1 ms interval in vmPFC blocks allowed us to verify that any effect of SMA stimulation on MEPs using this interval was specific to SMA. Altogether, the experiment involved 6 inter-stimulation intervals, both in SMA and in vmPFC blocks: 1, 4, 6, 8, 12 and 15 ms.

The experiment was divided into 10 blocks of 42 trials (*i.e.*, 5 SMA blocks and 5 vmPFC blocks). Each block comprised trials with single-pulse (*i.e.*, TS only) and paired-pulse TMS (*i.e.*, CS+TS with the 6 intervals mentioned above), occurring in a randomized order. As such, within each block, a total of 6 trials was recorded for each of the 7 conditions (*i.e.*, single-pulse, and paired-pulse with 1, 4, 6, 8, 12 and 15 ms), leading to 30 trials per condition over the whole experiment. These high numbers are quite unusual for TMS studies (*i.e.*, which typically

involve 10 to 20 MEPs per condition; *e.g.*, see Arai et al. 2012; Beaulieu et al. 2016; Derosiere et al. 2019; Neige et al. 2017). Having a large number of MEPs reduces within-subject variability and may help increase the reliability of the findings (Beaulieu et al. 2017; Chang et al. 2016). Finally, to prevent subjects from anticipating the stimulations, we varied the inter-trial interval, which ranged between 3.6 and 4.4 s (*i.e.*, rectangular distribution centered over 4 s; Rothwell et al. 1999).

Electromyographic recordings

Electromyography was used to record MEPs in the right FDI muscle. To do so, pairs of surface electrodes (Ag/AgCl, Medicotest, USA) were disposed on the FDI in a belly-tendon montage. A ground electrode was placed on the styloid process of the right ulna. EMG signals were recorded for 800 ms on each trial, starting and ending 400 ms before and after the TS, respectively. The signals were amplified with a gain of 1000, and band-pass and notch-filtered (10−500 Hz and 50 Hz, respectively) online using a dedicated amplifier (Digitimer D360; Digitimer Ltd., Welwyn Garden City, UK). Signals were digitized at a sampling rate of 2000 Hz (CED Power 1401; CED Ltd., Cambridge, UK) and collected using the Signal software (version 6.04; CED Ltd.) for further offline analyses.

Data analyses

EMG data were analyzed with custom Signal and R scripts (R Core Team, 2020). Of note, to prevent contamination of the MEP measurements from background muscular activity, participants were reminded to relax during the whole experiment based on the EMG signals, which were continuously screened by the experimenters. In addition, trials in which the root mean square of the EMG signal exceeded 2.5 SD above the mean before stimulation (*i.e.*, -250 to -50 ms from the pulse) were discarded from the analyses. Besides, to attenuate any effect of MEP variability on our measures, MEPs with an amplitude exceeding 2.5 SD around the mean within a given condition were excluded too. Following this cleaning procedure, we had 84.9 ± 7.55 % and 86.63 ± 5.53 % trials left on average for SMA and vmPFC blocks, respectively.

We then extracted the peak-to-peak MEP amplitude for each subject, each condition and each single trial. Trials were subsequently pooled together, by computing the median amplitude for each subject and each condition. The nature of the influence of the SMA / the vmPFC over M1 (*i.e.*, facilitatory *vs*. suppressive) was finally quantified by computing a ratio expressing

MEPs elicited by the TS in paired-pulse trials relative to MEPs elicited in the TS in single-pulse trials (Derosiere et al. 2020; Koch 2020; Lafleur et al. 2016; Neige et al. 2021). Following this procedure, one MEP ratio was obtained for each subject and each inter-stimulation interval. MEP ratios above 1 were taken as a marker of a facilitatory influence of the conditioned area on M1, whereas ratios below 1 were considered as reflecting a suppressive effect on M1.

Statistical analyses

All statistical analyses were performed using the JASP software (JASP Team, version 0.14.1.0; https://jasp-stats.org/). Data were normally distributed, as evidenced by non-significant results of the Shapiro-Wilk tests. When running repeated-measures (rm)ANOVA, Mauchly's tests were systematically exploited to check for data sphericity and a Greenhouse-Geiser correction was applied if the sphericity assumption was violated.

First, we aimed to identify whether the influence of the CS on MEP amplitudes varied as a function of the inter-stimulation interval (*e.g.*, whether the effect for an interval of 1 vs. 4, 6 and 8 ms differed for SMA blocks; see section *Inter-stimulation intervals and blocks*, above). To address this point, MEP ratios obtained for SMA and vmPFC blocks were analyzed using two separate one-way rmANOVAs with INTERVAL (1, 4, 6, 8, 12 and 15 ms) as a within-subject factor. Pre-planned post-hoc analyses were performed on significant interactions after applying a Bonferroni correction for multiple comparisons. Effect sizes were estimated for the main effect of INTERVAL, by calculating partial eta squared (η^2_p). In accordance with conventional interpretation partial η^2_p, a value of 0.01 is interpreted as indicating a small effect size, a value of 0.06 a medium effect size and a value of 0.14 or more as a large effect size (Lakens 2013). Second, we sought to determine whether the CS had a significant facilitatory or suppressive effect on MEP amplitude. To this aim, MEP ratios were compared against a constant value of 1 (*i.e.*, reflecting the amplitude obtained in TS only trials) using one-sample t-tests, as usually performed in TMS studies (Arai et al. 2012; Neige et al. 2020; Quoilin et al. 2019; Wang et al. 2020).

To complement the frequentist statistics, we conducted a Bayes factor (BF) analysis, allowing us to quantify statistically the level of evidence for the presence of an effect on MEP ratios. These analyses were performed using the JASP default parameters (*i.e.*, Cauchy prior width of 0.707; van Doorn et al. 2021). BFs (expressed as BF_{10}) provided us with a ratio of the

likelihood probability of the alternative hypothesis (*i.e.*, H_1: the probability that data exhibit the effect; Morey and Rouder 2011) over the null hypothesis (*i.e.*, H_0: the probability that data do not exhibit an effect of the tested factor). A BF_{10} of 1 reflect an equal probability that H_1 and H_0 are correct, whereas a value higher than 1 would reflect a higher probability that H_1 is correct. In accordance with conventional interpretation of BF values (Jeffreys, 1961), a BF_{10} value ranging between 1 and 3 is interpreted as indicating anecdotal evidence in favor of H_1, a value between 3 and 10 as indicating substantial evidence for H_1, a value between 10 and 30 a strong evidence for H_1, a value between 30 and 100 a very strong evidence for H_1, and a value above 100 a decisive evidence for H_1. Conversely, a BF_{10} value between 0.1–0.33 and 0.33–1 indicates substantial and anecdotal evidence for the null hypothesis, respectively.

Results

SMA stimulation induced a mix of facilitatory and suppressive effects on MEP amplitudes depending on the inter-stimulation interval

Figures 2.A and B illustrate the MEP ratios obtained as a function of the inter-stimulation interval for SMA blocks. Interestingly, the rmANOVA revealed a main effect of the factor INTERVAL on MEP ratios (GG-corrected $F_{(2.41,45.87)} = 10.75$, $p < .0001$). The n^2_p for this effect was .361, denoting a large effect size. Further, the BF_{10} was 560807, indicative of a 'decisive' evidence in favor of H_1 (*i.e.*, H_1: presence of an effect of INTERVAL) over H_0 (*i.e.*, H_0: lack of effect of INTERVAL). Post-hoc analyses indeed showed that MEP ratios strongly varied as a function of the inter-stimulation interval: ratios for 6 ms ($p < .001$; $BF_{10} = 114.17$), 8 ms ($p < .001$; $BF_{10} = 87.44$), 12 ms ($p < .001$; $BF_{10} = 35.29$) and 15 ms ($p < .001$; $BF_{10} = 119.87$) were significantly higher than at 1 ms. Moreover, ratios for intervals of 8 ms ($p < .001$; $BF_{10} = 12.67$) and 12 ms ($p = .006$; $BF_{10} = 8.46$) were significantly higher than for an interval of 4 ms. Finally, the ratio at 12 ms was not significantly different from ratios obtained at 6 ms ($p > .999$; $BF_{10} = 0.603$) and 8 ms ($p > .999$; $BF_{10} = 0.261$) intervals, nor was the ratio at 15 ms when compared to 6 ms and 8 ms intervals ($p > .999$, $BF_{10} = 0.246$ and $p > .999$, $BF_{10} = 1.235$, respectively). Altogether, these findings indicate that the facilitatory effect of SMA stimulation reported in the literature using classical, short intervals (*i.e.*, 6 to 8 ms; Arai et al., 2011, 2012; Green et al., 2018; Rurak et al., 2021) was significantly stronger than when using a 1 ms interval. Further, the similarity of MEP ratios obtained with intervals of 6-8 ms and of 12-15 ms suggests that

the facilitatory effect of SMA stimulation reported for short intervals – supposed to probe cortico-cortical circuits – was also present at longer intervals – probing cortico-subcortico-cortical circuits preferentially (Neubert et al., 2010).

As mentioned above, to test directly whether the CS had a significant facilitatory or suppressive effect on MEP amplitudes, MEP ratios were compared against a constant value of 1 using one-sample t-tests. Interestingly, this analysis confirmed the presence of a significant facilitatory influence of SMA stimulation on MEP amplitudes (*i.e.*, MEP ratios > 1) for classical, short intervals of 6 ms (t_{19} = 2.161, p = .044; BF_{10} = 1.55) and 8 ms (t_{19} = 2.766, p = .012; BF_{10} = 4.32), in accordance with the literature. Most importantly, a similar facilitatory effect was found for 12 ms (t_{19} = 2.435, p = .025; BF_{10} = 2.42). As such, 75, 70 and again 75 % of subjects presented a MEP ratio above 1 at 6, 8 and 12 ms, respectively, implying that SMA stimulation potentiated MEP amplitudes for most of the subjects with these intervals (see Figure 2.C). Finally, another interesting finding revealed by the t-tests was the presence of a significant suppressive influence of SMA stimulation on MEP amplitudes for the 1 ms interval (t_{19} = 4.034, p < .001; BF_{10} = 49.39). In fact, 85 % of subjects presented a MEP ratio below 1 when using the 1 ms interval, implying that SMA stimulation had a suppressive effect for a very large proportion of subjects. Other t-tests failed to achieve the level of statistical significance (all p-values ranged between .070 and .081).

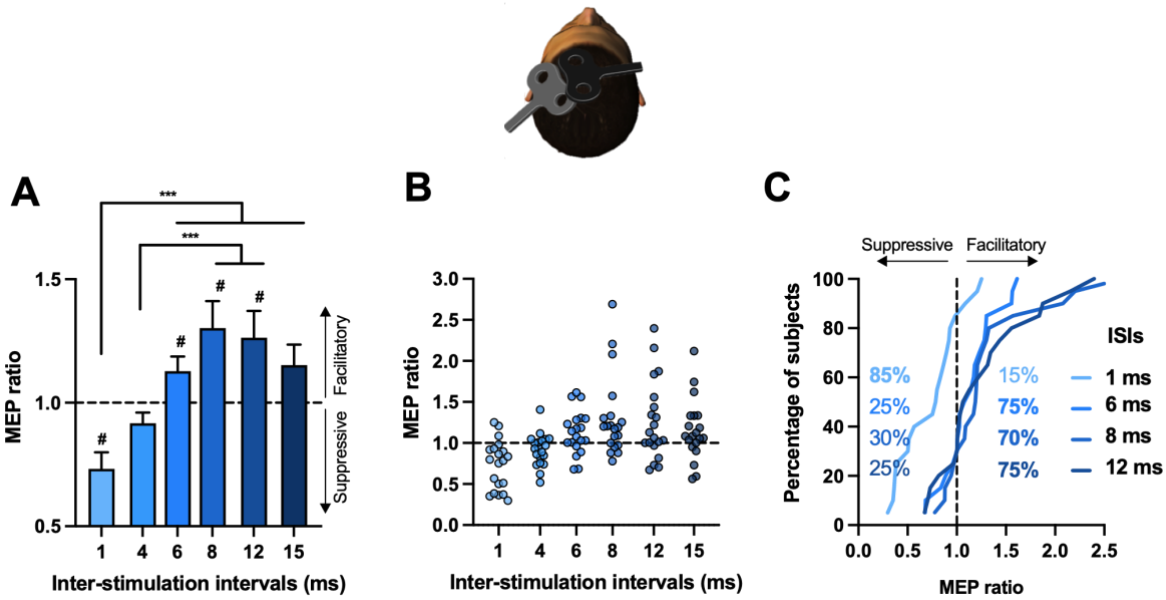

Figure 2: SMA stimulation induced a mix of facilitatory and suppressive effects on MEP amplitudes depending on the inter-stimulation interval. A. Group-averaged MEP ratios. Ratios above 1 indicate a facilitatory influence of SMA on M1, whereas ratios below 1 reflect a suppressive effect on M1. *** indicates significant differences between inter-stimulation intervals at p < .001). #

indicates a significant difference of the ratio with respect to 1. Error bars represent 1 SEM. **B.** Individual MEP ratios for each inter-stimulation intervals. **C.** Cumulative percentage of subjects for inter-stimulation intervals at which MEP ratios were significantly different than 1. 75, 70 and 75 % of subjects presented a ratio above 1 at 6, 8 and 12 ms, respectively (dark blue traces), while 85 % of subjects presented a ratio below 1 when using the 1 ms interval (light blue trace).

vmPFC stimulation induced a moderate suppressive effect on MEP amplitudes at some inter-stimulation intervals

Figures 3.A and B. illustrate the MEP ratios obtained as a function of the inter-stimulation interval for vmPFC blocks. The rmANOVA performed on MEP ratio did not indicate a significant main effect of INTERVAL ($F_{(1,19)} = 1.148$, P =.340, $n^2_p = .057$; $BF_{10} = 0.14$).

Despite this lack of main effect of INTERVAL, we tested whether the CS had a significant facilitatory or suppressive effect on MEP amplitudes at specific intervals (*i.e.*, by comparing ratios against a constant value of 1 with t-tests). Interestingly, this analysis revealed a significant suppressive influence of vmPFC stimulation on MEP amplitudes (*i.e.*, MEP ratios < 1) for short intervals of 6 ms ($t_{19} = -2.425$, p = .025; $BF_{10} = 2.38$) and 8 ms ($t_{19} = -2.201$, p = .040; $BF_{10} = 1.65$) as well as for a longer interval of 15 ms ($t_{19} = -2.370$; p = .029, $BF_{10} = 2.17$). Although the BFs for these effects provided anecdotal evidence in favor of H_1, a total of 75 %, 70 %, and 60 % of subjects presented a MEP ratio above 1 at intervals of 6, 8 and 15 ms, respectively, showing that vmPFC stimulation decreased MEP amplitudes for a large proportion of subjects with these intervals (Figure 3.C). Interestingly, other t-tests failed to achieve the level of statistical significance (all p-values ranged from .077 to .595), including for the ratio obtained with the 1 ms interval ($t_{19} = -0.541$, p = .595; $BF_{10} = 0.265$). The latter observation indicates that the suppressive effect observed with this interval was specific to SMA conditioning.

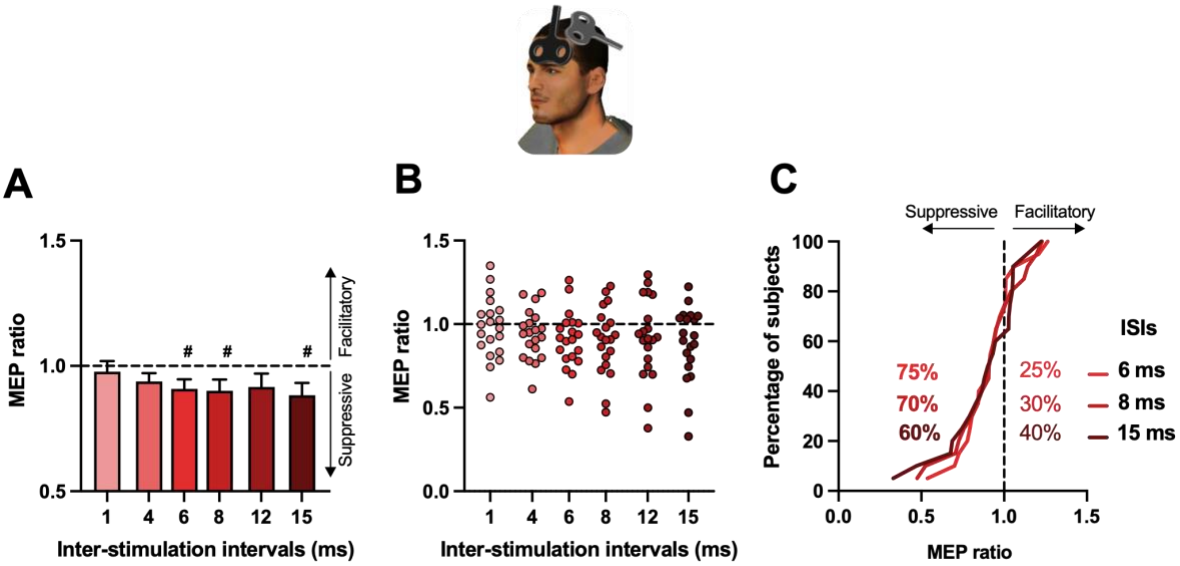

Figure 3: vmPFC stimulation induced a moderate suppressive effect on MEP amplitudes at some inter-stimulation intervals. A. Group-averaged MEP ratios. Ratios below 1 reflect a suppressive effect on M1. # indicates a significant difference of the ratio with respect to 1. Error bars represent 1 SEM. **B.** Individual MEP ratios for each inter-stimulation intervals. **C.** Cumulative percentage of subjects for inter-stimulation intervals at which MEP ratios were significantly different than 1. 75, 70 and 60 % of subjects presented a ratio below 1 at 6, 8 and 15 ms, respectively.

Discussion

Over the last two decades, dual-site ppTMS has been widely exploited in humans, with studies probing the causal influence of multiple fronto-parietal areas on M1. However, several important issues remain currently open, notably regarding the use of this approach on key areas of the medial frontal cortex – including SMA and vmPFC. The present study directly addressed three of these issues. First, we aimed to provide insights as regards to the influence of SMA stimulation on M1 activity with long inter-stimulation intervals (12 to 15 ms), presumed to recruit cortico-subcortico-cortical circuits (Neubert et al., 2010). Our data reveal that SMA stimulation potentiates MEP amplitudes significantly with a 12 ms interval, indicating the recruitment of circuits that bear a facilitatory influence on M1. Second, we sought to clarify whether the MEP potentiation reported in studies targeting SMA and M1 with short intervals (6 to 8 ms) can be taken as a pure measure of cortico-cortical connectivity between these areas or if it could in part reflect the summation of volleys descending from those on motoneurons at the spinal level. Here, we were able to replicate the MEP potentiation previously observed for such intervals. More importantly, our data show that this facilitation does not occur when using

a very short interval of 1 ms, assumed to recruit spinal circuits. Rather, we found a striking, suppressive influence of SMA stimulation on MEP amplitudes with this interval. Finally, we tested the feasibility of exploiting ppTMS to probe effective connectivity between vmPFC and M1 and, relatedly, we determined the influence of vmPFC stimulation on motor activity. We found that vmPFC stimulation induced a moderate suppressive effect on MEP amplitudes with both short and long inter-stimulation intervals. Interestingly, vmPFC stimulation did not alter MEP amplitudes with the 1 ms interval, indicating that the suppressive effect observed with this interval was specific to SMA conditioning.

As mentioned above, SMA stimulation induced a significant potentiation of MEP amplitudes with the 12 ms interval. This finding is not trivial as SMA projects to M1 through multiple cortico-subcortico-cortical circuits (Accolla et al. 2016; Nachev et al. 2008; Oswal et al. 2021), with some exerting a net facilitatory influence on motor activity (*e.g.*, the direct pathway of the basal ganglia) and others playing a suppressive role (*e.g.*, the indirect and hyperdirect pathways). Here, one possibility is that SMA stimulation preferentially recruited the direct pathway of the basal ganglia. In this pathway, areas of the frontal cortex (including SMA) rely on their projections to the striatum to inhibit the internal segment of the globus pallidus, which itself suppresses neural activity in the subthalamic nucleus (Alexander and Crutcher 1990; Aron et al. 2007; Calabresi et al. 2014; Niranjan et al. 2018). The latter structure bearing a suppressive influence on the motor system (Aron et al. 2016; Frank 2006; Quartarone et al. 2020), the recruitment of this whole circuit eventually leads to a disinhibition of M1, putatively explaining the MEP potentiation observed with a 12 ms interval. Interestingly, the potentiation did not reach statistical significance when using an interval of 15 ms, indicating that the facilitatory effect uncovered here is interval-dependent, with an optimal temporal window of about 12 ms. The latter observation is relevant for future ppTMS studies aiming at probing these circuits.

Of note, we were able to replicate the MEP potentiation previously observed for intervals of 6 and 8 ms (Arai et al. 2011, 2012; Green et al. 2018; Rurak et al. 2021). More importantly, our data show that this facilitatory effect does not arise when using a very short interval of 1 ms, presumed to recruit spinal circuits. Hence, it is sensible to assume that the MEP potentiation reported in ppTMS studies using intervals of 6 to 8 ms does not result from the summation of excitatory volleys descending from SMA on motoneurons. In fact, we found a suppressive influence of SMA stimulation on MEP amplitudes when using the 1 ms interval, which was present in up to 85 % of the subjects. Although this effect was quite unexpected, a closer look

at the literature reveals that a similar reduction in MEP amplitudes could also be observed when stimulating the primary somatosensory cortex ipsilateral to the targeted M1 with a 1 ms interval (Brown et al. 2019). Interestingly, the primary somatosensory cortex also presents pyramidal cells that project to the spine. Still, this does not explain the reduction of MEP amplitudes. A potential explanation may come from the fact that corticospinal cells do not exclusively synapse onto motoneurons through direct, excitatory connections, which in reality represent only a minority of cortico-motoneuronal connections (Lemon 2008). Rather, a large proportion of cells binds to motoneurons through complex inhibitory circuitries. The SMA, for instance, innervates a specific set of spinal interneurons (Cheney et al. 2004). One possibility is that SMA stimulation led to the recruitment of inhibitory interneurons, decreasing the excitability of motoneurons and ultimately reducing the amplitude of MEPs elicited following M1 stimulation. As highlighted above, our data show that the stimulation of vmPFC – which does not present pyramidal cells – did not reduce MEP amplitudes when using the 1 ms interval. Similarly, we showed in two previous studies that conditioning the M1 contralateral – which present pyramidal cells that mostly project to the other side of the spine – to the M1 receiving the test stimulation with a 1 ms interval do not alter MEP amplitudes neither (Grandjean et al. 2018; Vassiliadis et al. 2018). Altogether, these findings indicate that the suppressive effect observed with a 1 ms interval occurs specifically when stimulating areas that present pyramidal cells *and* project to the same side of the spine as the targeted M1.

Another central aim of the current study was to test the feasibility of exploiting dual-site ppTMS to probe effective connectivity between vmPFC and M1, and to determine the influence of vmPFC stimulation on motor activity. In fact, while former investigations on caudal areas of the medial frontal cortex (*i.e.*, SMA and preSMA) generally reported a facilitatory influence on M1, ppTMS studies on more rostral areas of the frontal lobe, such as the dorsolateral PFC, revealed the operation of suppressive circuits (Wang et al. 2020). Here, we found that vmPFC stimulation moderately decreases MEP amplitudes at specific short and long inter-stimulation intervals. This finding suggests the existence of two frontal regions with opposite influences on the motor system at rest, with more caudal areas – *e.g.*, SMA and preSMA – bearing a facilitatory influence preferentially, and more rostral ones – *e.g.*, vmPFC and the dorsolateral PFC – exerting a suppressive impact. The opposite influence of these regions on M1 may allow them to implement distinct functional roles in motor behavior.

Although the present results are quite encouraging for future ppTMS studies, some methodological considerations must be mentioned. A first, important aspect is the inter-subject

variability of the response to the conditioning stimulation. Most noticeably, the suppressive effects of vmPFC stimulation on MEP amplitudes (*i.e.*, with intervals of 6, 8 and 15 ms) were highly variable across subjects and thus quite marginal at the group level, putatively due to the difficulty of reaching this area with the magnetic field. As mentioned in the introduction, a few repetitive TMS investigations have attempted to target vmPFC and produced mixed findings, with some succeeding in altering behavior (Kearney-Ramos et al. 2018) and others failing to do so (Codol et al., 2020). One possibility to enhance the recruitment of vmPFC neurons would be to adjust the intensity of the conditioning stimulation according to the individual scalp-to-cortex distance (Stokes 2005; Stokes et al. 2007, 2013) as previously done in repetitive TMS studies (Hanlon et al. 2017; Kearney-Ramos et al. 2018) Such an adjustment could lead to a 10–30 % increase in intensity given the greater scalp-to-cortex distance for most prefrontal regions relative to M1 (Kähkönen et al. 2004). Still, this issue warrants further studies, as the application of a high intensity stimulation at this frontopolar location may be particularly uncomfortable for the subjects. A second, critical aspect to consider is the coil placement. This is especially true when stimulating SMA, because of its spatial proximity with M1. Here, we used a neuronavigation system to target the MNI coordinates of the SMA based on individual MRI images. In the majority of the subjects (n = 12 / 20), we had to slightly adjust the M1 stimulation site (*i.e.*, the hotspot) and its corresponding rMT. To the best of our knowledge, this type of adjustment has never been reported to date, despite the existence of multiple ppTMS studies on areas lying close to M1. For the sake of transparency, we think that future studies should systematically report any adjustment of coil locations.

Overall, the current study shows that SMA and vmPFC conditioning induce a mix of facilitatory and suppressive influences on motor activity. Our findings pave the way for both fundamental and clinical investigations aiming at understanding the causal role of these areas in the modulation of motor activity, as may occur in motor planning, decision-making, and inhibitory control, in which SMA and vmPFC play a central role.

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Declaration of interests

The authors declare no competing interests.

Data Availability

All datasets will be freely available on the Open Science Framework repository upon publication at https://osf.io/up45j/

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